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Functional Immune Anatomy of the Liver - as an allograft

By

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Key words:

Abbreviations: APC: antigen presenting cell; BEC: biliary epithelial cells; DC: dendritic cells; DCD: donation after cardiac death; DSA: donor-specific antibodies; ECD: extended criteria donor; HA: hepatic artery; HABR: hepatic arterial buffer response; HBV: hepatitis B virus; HCV: hepatitis C virus; HMS: hepatic microcirculatory unit; HSC: hepatic stellate cells; LSEC: liver sinusoidal endothelial cells; KC: Kupffer cell; MAMP: microbial-associated molecular patterns; MHC: major histocompatibility complex; MPS: mononuclear phagocytic system; NK: natural killer; PCP: peribiliary capillary plexus; PCS: post-capillary sinus; TCMR: PFbs: portal fibroblasts; PV: portal vein; T cell-mediated rejection; TLR: toll-like receptors;

ABSTRACT

The liver is an immunoregulatory organ in which a tolerogenic microenvironment mitigates the relative “strength” of local immune responses. Paradoxically, necro-inflammatory diseases create the need for most liver transplants. Treatment of HBV, HCV, and acute TCMR have redirected focus on long-term allograft structural integrity. Understanding of insults should enable decades of morbidity-free survival after liver replacement because of these tolerogenic properties.

Studies of long-term survivors show low-grade chronic inflammatory, fibrotic and microvascular lesions, likely related to some combination of environment insults (i.e. abnormal physiology), donor-specific antibodies, and T cell-mediated immunity. The resultant conundrum is familiar in transplantation: adequate immunosuppression produces chronic toxicities, while lightened immunosuppression leads to sensitization, immunological injury, and structural deterioration. The “balance” is more favorable for liver than other solid organ allografts. This occurs because unique hepatic immune physiology and provides unintended benefits for allografts by modulating various afferent and efferent limbs of allogenic immune responses.

This review is intended to provide a better understanding of liver immune microanatomy and physiology and thereby: a) the potential structural consequences of low-level, including allo-antibody-mediated injury; and b) how liver allografts modulate immune reactions. Special attention is given to the microvasculature and hepatic mononuclear phagocytic system (MPS).

INTRODUCTION

The liver is an immunoregulatory organ (1-5) in which a tolerogenic microenvironment mitigates the relative "strength" of local immune responses. Paradoxically, necro-inflammatory diseases still create the need for most liver transplants. Effective anti-HBV(6, 7) and anti-HCV(8, 9) medications and control of acute TCMR have, or will shortly, largely eliminate the negative impact of these insults, redirecting therapeutic focus toward long-term allograft structural integrity. Perhaps a better understanding of unaddressed insults will widely enable decades of morbidity-free survival after liver replacement.

Indeed, emerging evidence shows low-grade chronic inflammatory, fibrotic and microvascular lesions, which are likely related to some combination of environment insults (i.e. abnormal physiology), donor-specific antibodies (DSA), and T cell-mediated immunity, are associated with suboptimal immunosuppression and chronically threaten architectural integrity. The resultant conundrum is familiar in transplantation (reviewed in (10)): adequate immunosuppression reliably produces chronic toxicities, while lightened immunosuppression often leads to sensitization, immunological injury, and structural deterioration. The "balance", however, is substantially more favorable for liver than other solid organ allografts.

Liver immunology (1-5, 11, 12) and liver allograft "tolerogenicity" (13-15) are the subject of excellent recent reviews, but two areas remain incompletely addressed: the biliary tree and antibodies as immunological effectors and modulators, included herein.

IMPORTANT DIFFERENCES BETWEEN LIVER AND OTHER SOLID ORGAN ALLOGRAFTS

1) The liver can be viewed as two inter-dependent organs with a dual afferent blood supply:
    a. biliary tree: "centrally-placed" tissue whose health is critical to parenchymal integrity. Supplied by arterial blood draining into a typical capillary network, which like kidney and heart, is susceptible to ischemic and immunological insults(Figure 1).
    b. hepatic parenchyma: the bulk of liver mass which envelops the biliary tree and contributes greatly to tolerogenicity. Supplied by partially de-oxygenated low pressure portal venous blood, rich in intestinal bacterial products and pancreatic hormones, feeds into a unique sinusoidal bed(Figure 2).
2) Constant exposure to intestinal microbial products fosters a "tolerogenic" microenvironment with relatively low co-stimulatory and MHC class II expression on antigen presenting cells (APC), including the endothelium (2, 5, 12, 16, 17).
3) Sinusoids are the majority microvasculature, lined by LSEC and KC (2, 5, 12, 16-19), which scavenge particulates/antigens, and regulate immune responses (2, 5, 12, 16-18, 20-22), liver regeneration(23-25), and fibrogenesis(25, 26).
4) Tremendous parenchymal regenerative abilities include collagenase-mediated matrix remodeling (24, 27), which can reverse fibrosis (28, 29) after elimination of immune injury. This is not observed with other solid organ allografts(30).

5) A variety of immune leukocytes (classical T and B cells, NK, NKT, and γδ-T cells(31, 32)) are normal hepatic inhabitants, including hematopoietic stem cells (33, 34).

HEPATIC ARTERIAL BLOOD SUPPLY AND THE BILIARY TREE

More than seven arteries supply different bile duct territories, including the cystic, posterior superior pancreatico-duodenal, right and left hepatic, and retro- p ortal collectively providing 95% of arterial blood(35). Arteries encase the biliary tree as far as the peripheral branches, like ground vines around tree trunks(Figures 1 and 2). Flow is regulated by systemic pressure and intra-hepatic resistance vessels including pre-capillary sphincters (36, 37). Typical of splanchnic arterial systems, three anastomotic patterns occur on bile duct walls: a network, a longitudinal anastomotic chain, and an arterial circle(35).

Intra-hepatic portal tract hepatic artery branches divide into axial (accompanying) vessels (38, 39) that branch into peribiliary (connecting) arterioles (38, 39). These taper to form the peribiliary capillary plexus (PCP), which supplies bile ducts(38, 39) (Figure 2). The axial arteries also send capillary branches to: a) portal connective tissue; b) portal vein vasa vasorum; c) direct arterioportal anastomoses alongside septal venules supplying the lobules, from which regular short oblique arterioles enter the adjacent venule or sinusoids (panel 2 Figure 2) (38, 40); and d) isolated arteriolar branches that perforate deep into lobules, possibly supplying hepatic vein vasa vasorum and the liver capsule(41).

The PCP has 2 - 3 well-developed layers in large intrahepatic/extrahepatic bile ducts (42): inner, mostly afferent, subepithelial capillaries (like renal peritubular and cardiac interstitial capillaries); an intermediate and an outer, mostly efferent, layer (43) (Figures 1 and 2). Outer PCP layers end in post-capillary sinuses PCS) - slightly dilated endothelial conduits linking to sinusoids and portal vein branches (38, 39). PCP layers become ill-defined in smaller interlobular (<100 μm) bile ducts and attenuate to scattered capillaries: smaller interlobular bile ducts and ductules are accompanied by up to three CD34+ capillaries within <15μm from the basement membrane (42, 44).

Arterial/PCP insufficiency causes ischemic cholangiopathy(45-47). Deep PCP injury before transplantation predicts post-transplant biliary strictures in extra-corporally perfused livers(48-50). Chronic biliary disease(44) and chronic rejection(51, 52) reduce axial, connecting artery and PCP density around small interlobular (< 100 μm) bile ducts, analogous to heart and kidney allografts(53-55). Their destruction likely reflects imbalances between pericyte and edothelial cell repair (56, 57).

The Hepatic Artery Buffer Response (HABR) (Figure 3; HABR) refers to the reciprocal regulation between portal venous and hepatic artery flow. It is independent of innervation and normally suppressed by normal portal venous flow “washout” of the locally-produced major mediator and vasodilator, adenosine. Adenosine washout maintains physiological arterial constriction (58-61). Other mediators, such as nitric oxide, carbon monoxide, and H_2S are also likely HABR contributors (58, 59). Portal venous flow reduction (less washout), usually because of sclerotic occlusion, causes arterial dilation and compensatory increased lobular arterial blood flow via direct arterial conduits and arterio-venous anastomoses at lobular edges or arterial supply to lobules, discussed above. Interestingly, adenosine also can inhibit lymphocyte activation and/or promote Treg expansion(62). Chronic arterial compensation sustains hepatocyte viability/growth

causing nodularity, or nodular regenerative hyperplasia, common in long-surviving liver allografts(63). Conversely, portal venous hyperperfusion in small-for-size livers causes arterial vasospasm/constriction(58, 61). By contrast, reduced arterial perfusion does not alter venous flow, which is driven by splanchnic venous return.

BILIARY TREE

The centrally-placed biliary tree, lined by a single layer of biliary epithelial cells (BEC) under hormonal and neural control, is an excretory conduit for hepatocyte-synthesized bile, excretes enzymes and mucins, and modulates bile water content and composition (64, 65), which contains bile salts (61%) needed for fat emulsification/absorption; fatty acids (12%), cholesterol (9%), phospholipids (3%), bilirubin (3%), >250 proteins (7%), and other endogenous and exogenous compounds, including bio-transformed drugs (66, 67). BEC HCO_3^- secretion normally maintains an alkaline pH preventing the uncontrolled permeation and damage from hydrophobic bile salts, discussed below(68). Despite its importance to parenchymal health and participation in innate and adaptive immune responses (69-71), the biliary tree is usually overlooked in comprehensive liver immunology reviews (1-4, 11, 12). However, the high incidence (~20%) of complications (72-75) and susceptibility to AMR-mediated PCP damage (76-78) mandate greater attention in this review.

Intra-hepatic and hilar/extra-hepatic biliary tree development from hepatoblasts and hepatic diverticulum, respectively, is closely linked with arterial/PCP development(79), fusing into a seamless drainage conduit prior to birth (42, 79, 80). BEC and hepatocytes serve as progenitors for the intra-hepatic biliary epithelium(81, 82); extra-hepatic BEC renewal appears to depend on residual BEC and stem cells at the base of peribiliary glands(49, 83-85).

Secretory immunoglobulin A (sIgA) (86), synthesized by plasma cells near bile ducts (87, 88) dominates bile immunoglobulins (89), but IgG and IgM are also present (90, 91). They neutralize pathogens and bacterial toxins (92); complex with free antigens, facilitating excretion thereby reducing systemic responses (93, 94); and bind intracellular pathogens during transcytosis(95).

BEC possess an array of anti□microbial defenses, such as lactoferrin and lysozyme from peribiliary glands (96); defensin(97), cathelicidin(98, 99) and human β□"efensin 1 (hBD□1). Trefoil family factor proteins protect BEC by increasing mucous viscosity in large bile ducts and peribiliary glands(100□103). Others are inducible(104□106), such as hBD□2 in large bile ducts after infection (107). Some innate defenses also modulate adaptive immunity by recruiting CD4+ T cells and immature dendritic cells(108).

BEC also express TLR (71) whose ligation triggers cytokine elaboration to recruit and activate T-cells, macrophages, and NK cells. Human BEC also constitutively express IL-8 and MCP-1 (109-112) - important chemotaxins for neutrophils, monocytes, and T cells – and further upregulate these after endotoxin (via TLR4) or inflammatory cytokine exposure (although IFN-γ inhibits IL-8 production). These and other inflammatory cytokines increase BEC immune "visibility" by increasing constitutive ICAM-1, LFA-3, MHC I and II (70, 71, 113-118) and the molecular machinery for non-professional APC functions, including co-stimulators CD80/CD86 (70, 117-120). This enables BEC to elicit recall responses in primed T cells (116, 121, 122), but not naive T-cell activation (123). Some dampening of immune responses is also possible as PDL1 and PDL2 are also induced by IFN-γ (124).

Ischemic, immunological, and technical insults damage BEC and bile ducts (21, 125, 126). Preservation/reperfusion injury in DCD and ECD donors cause PCP microvascular thrombosis and ischemia (127-129). Re-oxygenation causes more damage than hypoxic injury (130), which enhances BEC TRAIL-mediated apoptosis (131). Immunological injuries include direct cytotoxic lymphocytic damage and indirect ischemic damage from disruption of the PCP by DSA or isoagglutinins (78, 130, 132-137). Pathogenic mechanisms involved in antibody-mediated PCP damage are similar to those described for kidney and heart allografts(138, 139). BEC apoptosis can be autocrine, paracrine and/or leucocyte-mediated (TNF-α, Fas/FasL, TNF-related apoptosis-inducing ligand (TRAIL)) (140-145), but susceptibility can be further modulated by bcl-2 family members.

Inner PCP destruction and local micro-environmental disruption likely account for poor BEC wound healing(74, 146) resulting in ischemic cholangiopathy(reviewed in (74, 147-149)). Necrotic BEC and senescence-associated secretory phenotypes (SASPs)(150) impede wound healing by promoting inflammation and subsequent stricturing(151, 152). Suboptimal BEC regeneration might also contribute (72, 153, 154).

Bile composition influences wound healing: hydrophobic bile salts at low concentrations elicit BEC ROS resulting in apoptosis(72) and necrosis(155); conversely, hydrophilic bile salts (e.g. ursodeoxycholic acid(UDCA)) protect BEC from hydrophobic bile salt-induced injury (reviewed in (155)). UDCA improves liver injury test profiles and the incidence of early biliary tract complications (156, 157). Ischemic injury also impairs HCO_3^- secretion (130, 131, 136, 158) increasing susceptibility to hydrophobic bile salt injury.

PORTAL VENOUS BLOOD SUPPLY AND THE "TOLEROGENIC" PARENCHYMA

Large proximal conducting portal veins (>0.3mm diameter) give rise to smaller hierarchically branching parenchymal/distributing veins responsible for substance exchange with hepatocytes and maintaining liver microarchitecture (159, 160). The conducting, but not the parenchymal, portal vein branches are mirrored with corresponding hepatic veins that drain sinusoids into inferior vena cava (160).

Parenchymal veins follow a strict branching pattern: each first order branch supplies ~1mm^3 venocentric parenchymal mass and begets 11 perpendicular, second-order branches that lie in terminal portal tracts on light microscopy (the classic portal triad (159)). These branches outnumber hepatic vein branches 6:1, creating the "classic" hepatic lobule (Figure 2) demarcated by portal tracts at vertices of a hexagon surrounding a central vein. Afferent portal venous blood periodically exits portal tracts to travel along the hexagon edges in *septal venules*. Together they align successively as seams across a curtain of intervening anastomosing sinusoids along an interlobular "vascular septum" (159, 160) from whose face blood flows towards the hepatic veins(Figure 2).

Venous blood first enters the vascular septum sinusoids at right angles from the septal venules through short CD34+ *inlet venules,* which retain a classical basement membrane. The hepatic microcirculatory subunit (MHS), cholehepaton, or primary lobule is the functional nephron equivalent (161): a hepatocyte cone supplied by one inlet venule and draining bile into one bile duct (Figure 2) (159, 161, 162). Flow from inlet venules feeds a distributing network of sinusoids (see (Figure 2a)) (septal zone of inflow, sandwiched between consecutive septal venules). From that inflow zone surface (estimated at 1.7 m^2 total) the distributed flow enters the

remainder of the lobule like a “wave front” into radial sinusoids (Figure 2b) to exit the lobule at terminal hepatic veins.

Sclerosis of portal, septal, and/or inlet venules may be attributable to chronic immunosuppression(63), DSA(135, 163, 164), or other insults, often manifests as NRH(63) via the HABR, in long-surviving grafts(165, 166). Portal inflammation with “interface hepatitis” associated with de novo DSA in long-surviving liver allograft recipients(135, 163, 164, 167) might represent mononuclear septal or inlet venulitis, but work is needed to mechanistically clarify the association.

Liver Sinusoidal Endothelial Cells (LSEC)

LSEC comprise ~50% of non-parenchymal liver cells and channel blood from portal vein branches into “central veins” – the smallest efferent hepatic veins. They interface between sinusoidal content and Disse’s space (Figure 4), into which they regulate leukocyte transmigration with induction of adhesion molecules. Transcellular fenestrations (*fenestrae*, Latin for window; average ~100 nm in diameter): a) are arranged in distinct groups (sieve plates); b) occupy ~6-10% of the surface area (168); c) lack diaphragms, or proteinaceous “screens” that create a selectively permeable barrier to particulates; and d) change size/diameter to modulate bidirectional flow of particulates (e.g. chylomicron remnants and lipoproteins), cells or cell processes(5). LSEC renew from local expansion of liver-based progenitors and bone marrow precursor recruitment after severe injury or partial hepatectomy(23).

Steady state LSEC express vascular (e.g. CD31, $vWF^{negative\ to\ low}$, Ulex lectin binding, and CD105(169)) and lymphatic endothelial markers (CD31, LYVE-1, VAP- 1, and Reelin) (169, 170), generate lymph(171), and lack a typical basement membrane. LSECs also show innate and adaptive immune responsiveness, expressing multiple TLR, MHC I and II (normally at low levels), co-stimulatory molecules (CD80, CD86) and adhesion molecules (ICAM-1) (reviewed in (5)). LSEC internalize soluble antigens, immune complexes and other particulates (5, 172-174), which enables them to compete with DC for pathogen monitoring (reviewed in (5, 17)). In steady state or mild injury, cross-presentation of blood-borne antigens can cross-tolerize CD8+ T cells and promote expansion of regulatory T cells (5, 17). Conversely, innate danger signals (viral RNA, CpG DNA, activated complement, FcR engagement) can override “tolerogenic” tendencies, switching LSEC to recruit and directly stimulate CD8+ and CD4+ effector T cells (5, 17). They also have the potential to influence liver regeneration and fibrosis(12, 17, 23, 25, 26, 175).

Injury (26, 176-180), fibrogenesis (26, 169, 176, 178), and aging (181-183) cause LSEC changes referred to as “(pseudo-)capillarization” including defenestration, basement membrane deposition (type IV collagen, laminin, and fibronectin(178, 184, 185)), antigenic modulation (neo-expression or upregulation of CD31, CD34, vWF), inability to quiet stellate cell activation(23, 26, 177), altered hepatic lipid processing(175), and impaired cell-cell communication(26, 175, 177, 178). Immunohistochemical monitoring in operationally tolerant liver allograft recipients(186) can detect early LSEC changes, such as capillarization and nearby SMA+ SC activation, before more significant damage occurs (185-187).

Lymphatic Flow: The liver is the largest lymph producer: ~25-50% of thoracic duct lymph(188) accepting fluid from portal, sublobular, and capsular networks (171, 188-191). Most lobular lymph is initially formed in Disse’s space with a smaller PCP contribution (~10%) (171, 188-191) moving toward portal tracts(171, 189, 192)

where protruding collagen fibers delineate conduits to intra-portal terminal lymphatic capillaries (171) (Figures 2 and 4). Terminal lymph capillaries lack a continuous basement membrane, similar to LSEC, and are lined by endothelial cells that: a) express numerous but non-exclusive markers, (reviewed in (171, 193)); b) are anchored to surrounding collagen and elastin fibers (171); and c) facilitate fluid and cell entry via specialized intercellular junctions that restrict reflux (171, 188-191, 194). These coalesce into muscular conducting vessels that empty into hilar lymph nodes(171, 188-191). Perivenular lymph likely travels along similar collagen bundles (171, 188-190, 192, 194) into terminal lymphatic capillaries in sublobular vein walls that drain into subdiaphramatic nodes(171, 189, 190, 192) (see below).

Lymphatic ligation at transplantation initially results in intra-peritoneal DC-rich chylous leakage (1-3 liters/day) then directed to regional diaphragmatic nodes (195). Lymphatic drainage spontaneously regenerates after some months (196), but the effect on DC activities is unknown.

Hepatic Veins: This post-sinusoidal drainage system accepts sinusoidal blood beginning at terminal hepatic veins/venules or central veins located at the center of the lobular hexagon. Progressive coalescence of branches mimicking conducting, but not distributive, portal veins produces the classical lobule. These drainage conduits are targeted in both TCMR and AMR, perhaps related to local DC and terminal lymphatics (197, 198).

MAJOR BLOOD GROUP AND HISTOCOMPATIBILITY COMPLEX ANTIGEN EXPRESSION AND ORGAN CHIMERISM

Recognition that de novo anti-MHC DSA can decrease graft survival, especially when inflammatory comorbidities like recurrent HCV exist renewed interest in MHC antigen expression (76, 199-201). Cataloging tissue MHC antigen expression and organ composition/chimerism after transplantation demonstrates potential targets for anti- MHC DSA and the effect of donor-recipient MHC non- identity between various cell populations (e.g. recipient T cell-donor LSEC).

Immunohistochemistry staining of “normal” livers (donors, incidental operative biopsies, etc.) shows strong, diffuse, ABO and class I MHC antigen expression on all cells, albeit the latter is weaker on hepatocytes (202-214) (Table 1). Liver MPS cells also show MHC class II staining, but weaker than similar cells within other organs (2, 12, 16), with DQ being weakest(202-215). Portal and central vein and hepatic artery endothelium is normally class II negative. Precise descriptions for PCP, lymphatic and inlet venule endothelia are lacking, but portal capillary endothelial class II expression appears weaker and patchier than renal peritubular (203, 216) or heart interstitial capillaries(203, 217). Possible explanations include class II downregulation by IL-10 and prostaglandins from endotoxin-stimulated Kupffer cells (2, 218, 219). Although PCP are fed by the systemic circulation, they are bathed in lymph fluid produced in the sinusoids. However, more work examining specific compartments is needed.

Inflammatory stimuli (esp. γ-interferon) heighten MHC class I expression and induce class II in endothelia, BEC, and hepatocytes (DR>DP>DQ) (202-215). Practical consequences include variable DSA targeting, immune stimulatory capability, and effector efficacy dependent on immune complex density (139, 220, 221) provoked by co-existent pathology (e.g. TCMR, HCV) (76, 199-201) providing the potential for improved outcome with target antigen modulation (222, 223).

Recipient bone marrow-derived hematolymphoid cells (e.g. lymphocytes, macrophages/Kupffer cells (224-229), and dendritic cells) replace the majority of donor equivalents within months after transplantation (210, 225, 226, 230). Yolk sac-derived KC replacement confounds steady state ontogenic classification (231)), but microenvironmental influences reprogram chromatin to largely match tissue-specific identities of the original embryo-seeded population (232). Whether allograft disease, immunological mismatch or immunosuppression affects that "naturalizing" process is unknown, but intuitive.

Stellate and myofibroblastic cells can arise from BM-derived precursors(233, 234) and might contribute up to ~12% of myofibroblasts in sex-mismatched liver allografts(235), but few studies critically address this question. Initial enthusiasm for reports of recipient-derived hepatocytes and BEC in allografts (236, 237) dwindled when subsequent data questioned its magnitude (229, 230, 238-240).

Most reports suggest no/sparse replacement of the donor endothelium (226, 228-230, 241, 242); the few that differed (237, 243) did not find a correlation with tolerance (243).

Hepatic stellate cells (HSC), portal fibroblast/myofibroblasts, and myeloid suppressor cells

HSCs (peri-sinusoidal cells, fat-storing cells, and lipocytes) comprise ~10% of all liver cells and are the major source of myofibroblasts and fibrosis(244-250). They reside in Disse's space, throwing out long cytoplasmic extensions (~40 μm)(251), and hold ~80% of Vitamin A and retinoid stores(252, 253). Depletion models (254) identify HSC as the main contributors to liver fibrosis (255, 256) (above portal fibroblasts and myeloid suppressor cells (257-259)) and so therapeutic approaches to arrest/reverse fibrosis target HSC(260-262).

Quiescent human HSC express vimentin and type III intermediate filament protein, suggesting a myogenic or fibroblastic origin (263). Quiescence is maintained in part by LSEC via VEGF-mediated nitric oxide (NO) production (264, 265). After liver injury or exposure to danger signals like endotoxin(266, 267), stellate cells activate, losing retinoid stores and trans-differentiating into proliferating, contractile myofibroblasts (α-smooth muscle actin (α-SMA)+) (244) that produce collagen, other ECM components and trophic factors (263, 268, 269).

HSC activate in two stages (246, 270). "Initiation" involves transdifferentiation, proliferation and migration to injury sites (271-275). "Perpetuation" involves autocrine and paracrine signals, the latter from damaged/apoptotic hepatocytes (including TGF-β1 and ROS), activated KC, inflammatory cells and altered ECM composition(246, 270, 276-279). Activated HSCs elaborate inflammatory cytokines and chemokines (280-288). Examples that facilitate fibrosis include neutrophil recruitment (IL8), facilitating recruitment of CD8+ T cells to porto-septal areas (CCL2) in chronic viral hepatitis (280, 282, 289-293).

Inflammatory cell-derived IL-17A induces HSC collagen type I expression directly and indirectly via TGF-β from KC (294). Together, these damage signals promote a relative predominance of tissue inhibitors of MMP (TIMPs) over metalloproteinases (MMPs), which favors net ECM deposition (295). Activated HSC (SMA+) have been used to predict fibrosis development in HCV+ allografts(296). If the injury resolves, HSC can revert to quiescence or delete by apoptosis (297-307).

Activated state persistence results in fibrosis progression (26, 308). Nevertheless, when injury resolves, immunomodulation by HSC can instead limit fibrogenesis(309) via: a) anti-inflammatory mediators such as IL-10 (287, 288); b)

expansion of FoxP3$^+$ regulatory T cells; c) apoptosis of CD4$^+$ and CD8$^+$ T cells in fibrosis areas (287, 310); and d) stimulation of hepatocyte NO synthesis (285, 311), which together lead to T cell suppression (312, 313).

Portal fibroblasts (PFbs): In contrast to HSC, PFbs (314), lack vitamin A autofluorescence, GFAP, NGFRp75 and synaptophysin expression (244, 314), but early after bile duct ligation/cholestatic injury (257), or isolation (315) activate and differentiate into myofibroblasts expressing α-SMA, fibulin-2, elastin, NTPDase2, Thy1 (314, 316-318) and ECM including collagen type I. PFbs likely contribute to non-biliary fibrogenesis (e.g. viral hepatitis, alcohol) (318), but much remains speculative because of difficulty to unambiguously discriminate them from activated HSCs (257-259).

Myeloid-derived suppressor cells (MDSC) are a heterogeneous bone marrow-derived population (319) identified in humans as CD11b$^+$ CD33$^+$MHC-DR^{low} cells(320). MDSC are induced by an inflammatory microenvironment (e.g. viral hepatitis (321-323)) and mediators (324, 325), or from peripheral blood mononuclear cells (PBMCs) by HSC (326). They potently suppress T cell function (327), while immunoregulatory functions likely affect fibrogenesis (255) including HSC fibrogenesis via IL-10 secretion (328), although probably with redundancy of effect (329).

THE MONONUCLEAR PHAGOCYTE SYSTEM (MPS)

Three nominal cell types comprise the human hepatic MPS: DC, monocytes and macrophages- resident and acquired (Figure 4). Innate and adaptive immune functions assisted by resident MPS cells are comprehensive, affecting hepatic responsiveness to immunological, toxicological, metabolic or preservation/reperfusion challenges and regeneration, fibrogenesis and fibrosis resolution (reviewed in (19, 330-332)). Macrophage reactions are conditioned by their tissue environment and they are often among initial responders to disease. Their broad response repertoire invites therapeutic targeting. Although broadly comparable among species, MPS cells also show significant genetic regulation, phenotype, and prevalence differences (333-338).

Resident macrophages are sculpted by tissue specialization: transcriptomic/marker diversity among resident macrophages from different tissues exceeds their divergence from other myeloid cell types (339, 340). Nevertheless, different resident macrophages and monocyte-derived macrophages share steady state transcriptional signatures largely related to phagocytosis (337, 339). Steady state liver resident KC and monocytes function as independent mature lineages (341), but in disease, phenotypic boundaries become blurred (342-344).

Dendritic Cells (DC) and other non-professional APC

Classical/myeloid and plasmacytoid DC, evolve from a common bone marrow-derived DC precursor independent of monocytes and depend on FMS-like tyrosine kinase 3 ligand (FLT3L) for local hepatic expansion (231, 345-347). KC steadily recruit circulating recipient DC precursors in the sinusoids, which migrate into Disse's space (348), and enter portal-based terminal lymphatic capillaries, followed by drainage to regional nodes (171, 349-351) (Figure 4).

Most DC reside in portal tracts and around central veins (197, 211, 352), perhaps related to pre-lymphatic collagen fiber tracts(171, 188-190, 192, 194).

Normal liver DC have low co-stimulator expression (347, 353, 354) and readily produce IL-10 after TLR4 ligation - a tolerogenic state encouraged by abundant tissue IL-10 and TGFβ and by direct contact with adjacent sinusoidal endothelium (355).

Donor DC remain capable of triggering immunogenic responses critical to TCMR, albeit less efficiently than lymphoid tissue-based DC (4, 347, 353, 356-359). Recipient T cells directly recognize allogeneic MHC on donor DC that migrate to recipient central lymphoid tissues (197, 360) and residual donor DC within the allograft (197). Mass donor DC and other leukocyte migration early after transplantation contributes to activation-induced deletion (361-365). Their long-term persistence might contribute to tolerance maintenance (366, 367). Recipient DC uptake alloantigen and indirectly present or acquire whole non-self MHC from donor DC by trogocytosis or exosome uptake and present it semi-directly (368, 369).

Plasmacytoid DC regulate NK cells and are usually tolerogenic (influenced by the gut microbiome (370)), but can activate CD4 T cells when strong innate activation signals are present. Plasmacytoid DC and mature $CD14^{dim}$ sentinel monocytes rove within sinusoids patrolling for virus. They react to engulfed or cytosolic virus sensed via TLR7 or TLR9 by secreting type I interferons (358) and accumulate in sinusoids during viral and non-viral liver disease (371-373). pDC may also be responsible for cytokine storm syndromes driven by viral activation of TLR (374).

"Non-professional" APC include LSEC, BEC, hepatocytes, KC, HSC, and MDSC (3). KC cross-present antigen captured from other cells (375), while MHC/MHC molecule transfer between different cells through trogocytosis or exosomes (MHC dressing) potentially enables a variety of unconventional antigen-specific activation or suppression of T cells in disease (368, 369). Interactions between non-professional APC and naïve CD8 T cells usually fosters tolerance due to low co-stimulation and inflammatory signaling needed for priming (reviewed by (376)), such that liver-activated CD8 T cells can be rapidly cleared by suicidal emperipolesis within hepatocytes (377) or by apoptosis (378).

However, liver macrophages can activate naïve CD4 T cells to sustain local functional CD8 T cell generation (379). Some monocyte-derived cells transmigrating from sinusoids, particularly post-phagocytic, acquire an immune regulatory transcriptome and phenotype resembling DC ("monocyte-derived DC" or "antigen-presenting macrophages") (380-383); differences from classical DC are not clearly defined (195, 231, 384).

Kupffer Cells (KC)

KC, ~15% of all liver cells, are relatively long-lived, resident, sinusoidal-based, tissue macrophages with 2-3 fold periportal predominance, where they tend to be larger and more phagocytic (385-387). Most KC in resting livers lie between or cling over LSEC (Figure 4) with anchors through larger fenestra, have a ruffled surface with processes extending to sample slow flowing sinusoidal blood (388) and derive from extra-embryonic yolk sac hematopoietic precursors (389, 390), whose progeny migrate to the liver and accommodate with local mciroenvironmental signals (232, 391). Short term, KC are stellate and immobile (392), but they redistribute over weeks to form granulomas after insults, with their sinusoidal place supplanted by recruited monocyte-derived cells (393). In the steady postnatal state mature rodents and perhaps human KC renew themselves as necessary (enhanced with IL4 (343, 394)) without requirement of other input sources such as bone marrow-derived

monocytes (395-400). KC, however, are replaced within months after transplantation (210, 225, 226, 230).

Hepatic microenvironmental signals determine the homeostatic set points and the KC response spectrum but they excel at capture and clearance, including: circulating particles (>230 nm (174, 344, 401, 402)), circulating bacteria (392, 393), and oxidatively damaged red cells and haptoglobin-haemoglobin complexes, expedited by scavenger receptors (403, 404). Opsonized particles and pathogens and immune complexes(405) are recognized via Fc and complement C3 receptors – primarily CRIg (406). KC manage steady state antigenic particle phagocytosis with tolerance: patrolling antigen-specific regulatory CD4 T cells arrest on KC and are activated (but CD8 T cells are not), inducing a KC-dependent systemic tolerance (344).

Bacteremia is cleared by direct engulfment or trapping and interaction with other innate defenses, such as platelets to encase the bacteria (407), or neutrophils, for which the KC surface becomes a platform to kill bacteria. Subsequent clearance of apoptotic neutrophils by KC may return it to the native tolerogenic state (408-410). After extensive phagocytosis, macrophages/KC may migrate to portal tracts (411).

Relative hepatic resistance to AMR is an incidental byproduct of vigorous KC clearance of alloantibody complexed with soluble MHC class I, along with activated complement and platelets (22); KC depletion reverses this resistance(20, 21, 412, 413).

Identification: KC are difficult to isolate from liver in a representative way (339, 414), rapidly alter phenotype upon extraction (415), display a liver microenvironment epigenetic dependence and are less well-studied than other tissue macrophages (343, 393). Although difficult to sensitively discriminate on routine histology (416), KC appearance yields clinically relevant clues: hypertrophy and ceroid-loading (suggests recent cell debris phagocytosis and marks injury sites (416)); phagocytosed bile or foamy macrophages (indicate cholestasis); iron accumulation; erythrophagocytosis; fusion; topographic association with specific inflammatory cells (e.g. eosinophilic microvasculitis in AMR).

There is no KC-specific immunophenotypic marker, but useful practical markers in formalin-fixed biopsies combined with morphological assessment include CD68 (417-421), CD163 (404, 417, 422, 423)) and 25-F9 (424, 425). CD68 also marks plasmacytoid DC, while CD68, CD163 and other general resting macrophage markers such as CD64 and MERTK are expressed on some monocytes/monocyte-derived cells (339, 426-431). KC immunophenotype is described for various immune markers in clinical biopsies of normal liver, back table biopsies or stable grafts (424, 425, 432-439) but discrimination from infiltrating monocyte-derived cells in disease settings is not always possible.

Proteomic-transcriptomic screening identify highly expressed immunohistochemical signatures of resting and stimulated macrophages: phagocytosis, redox control, adhesion, fibrinolysis, lipid metabolism, etc. (440). Some markers are pleiotropic (e.g. Galectin-3) or not macrophage-restricted (e.g. transglutaminase 2 and galectin-3: hepatocytes; CD206: sinusoidal endothelium), necessitating multiplex staining for macrophage-specific evaluation.

Monocyte-derived cells in the steady state: Circulating monocytes do not reflect those sequestered by the hepatic microcirculation (441, 442). Human and murine monocytes show broadly comparable maturing populations, but different proportions

and gene expression patterns (430, 442). In the steady state, predominantly immature CD14+ ("classical") circulating monocytes arrest and transmigrate into Disse's space, acquiring increased MHCII; the majority patrol extravascular tissue as phagocytes with an anti-inflammatory tolerogenic phenotype (reduced response to LPS; suppressive of T cell activation) (443). Most such transmigrated monocytes probably traffic to afferent portal tract lymphatics and on to regional lymph nodes (427). Less mature monocytes (CD14+) may pass through the sinusoids and exit in hepatic venous blood, or may arrest and transmigrate past sinusoidal endothelium (dependent on VAP-1, CX3CL1 and VCAM-1(444)). A minority reverse transmigrate back into the sinusoid, acquiring CD16, increased scavenger receptors (CD163 and CD206) and a pro-inflammatory immune-activating capacity to secrete γ-IFN and induce effector T cells (443).

Thus the sinusoidal endothelium fosters both recruitment and then functional and anatomic partitioning of monocytes into pro- and anti-inflammatory phenotypes. $CD16_{high}$ ("non-classical") intravascular monocytes are small motile cells that patrol endothelium for virus, sensed by TLR7 or TLR8 (445), analogous to murine sentinel microvascular monocytes (441) that perform low-grade endothelial particle scavenging (397, 441, 446) without differentiating to macrophages (339, 427). Tissue nucleic acid sensing via TLR7 elicits a mixed luminal capillaritis: monocytes cluster and engage neutrophils to kill adjacent endothelium, removing injured or infected cells (446). The fate of such $CD16_{high}$ intra-sinusoidal pro-inflammatory monocyte-derived cells is not clear, but may include further transmigration and lymphatic egress (447).

In normal liver and stable liver allografts, portal macrophages are scarce, except for occasional ceroid-laden post-phagocytic cells (448).

Monocyte reactions: MPS cells accumulate during liver inflammation (including TCMR) due to enhanced sinusoidal recruitment of circulating intermediate CD16+ monocytes, mediated by constitutive and induced ligands (224, 444). In fibrosis, leukocytes can also exit portal and septal venules (449, 450). Monocytes transmigrate and differentiate into proliferating macrophage infiltrates heterogeneous for various antigen presentation, cytokine secretion and phagocytosis activities (343, 381, 393, 436, 451-454). In acute TCMR activated macrophages accumulate in portal tracts (438), although perivenular, veno-occlusive and lobular hepatitic patterns of active TCMR exist (224, 437, 455-461). Indeed, KC hypertrophy and lobular macrophage infiltrates occur in TCMR, chronic rejection (437, 448, 462) and AMR (463-465). Inflammatory macrophages further contribute to chronic rejection by causing apoptosis of bile duct epithelium and hepatocytes via CD40-dependent mechanisms (437, 466). In severe TCMR, KC scavenge major basic protein (PRG2) from eosinophils (467), which are macrophage activators (468). TLR9-dependent reactions can augment viral immunity resulting in distinctive parenchymal monocyte-derived macrophage clusters that support effector CD8 T cell proliferation over several days with little hepatocellular injury (469).

Phenotypic macrophage diversity: The "immunologically activated macrophage" (470, 471) concept evolved from a non-specific microbiocidal state induced in antigen-dependent reactions to encompass "alternative activation" (e.g. helminth infection) and dichotomous polarization (M1 or M2 states; later with subtypes) based on culture changes after isolated stimuli. The linear model was revised to an activation spectrum (472, 473)): helpful to explore macrophage activities in culture,

but labels do not capture individual macrophage behaviors in tissue pathology (342, 472, 474).

Macrophages show transcriptional shifts as tissue responses wax and wane (338), and epigenomic memory affects subsequent responses on repeated stimulation(475). Transcriptomic analyses found 49 different gene co-expression clusters motivating a dozen or so inducible response states to soluble signals alone (476, 477). Stimuli segregated into those causing widespread or limited transcriptional changes from culture norms, but not along M1-M2 divisions (477). Genetic evidence also fails to identify distinct pre-committed macrophage subsets, although single cell-resolution studies in disease are lacking. Instead, transcriptomic, proteomic and multiplex marker data highlight process-orientated signatures that characterize maturational, and functional states (337, 340, 472, 478).

Inflammatory macrophage activation is coupled to obligate restraining tissue feedback systems involving macrophages themselves (intrinsic reprogramming), activated stellate cells, hepatocytes, mast cells and others (343, 454, 479-483). Inhibitory systems predominate when inciting stimuli diminish: incoming macrophages express increasing regulation (326), scavenging and repair signaling, and monocyte-derived macrophages and self-renewal replace depleted KC (343, 393, 454, 484).

“Activity” marker interpretation, therefore, requires context: MERTK is immunosuppressive, but tied to prior immune activation and TLR engagement which it attenuates safely (482). In this context, MERTK reflects immune activation, although by preventing endotoxic shock it is anti-inflammatory (485). Likewise, CD163+/HO-1+ haemophagocytes in macrophage activation syndromes and sepsis probably represent a compensatory anti-inflammatory response to excessive innate activation (374, 486-489). Therefore, characterization of ‘markers’ by downstream actions may not make sense if the upstream context and positioning of that response is ignored.

More complications arise when markers are pleiotropic (e.g. MERTK also promotes efferocytosis of dead cells by macrophages (490)). Such considerations might explain heterogeneity and “unorthodox” concurrence of culture-defined “macrophage polarity” markers in clinical disease infiltrates (342). More comprehensive multiplex profiling in diseased tissue sections might better reveal individual macrophage engagement (472).

TOLERANCE MECHANISMS

Through tolerance, potentially harmful responses to innocuous antigens from gut commensals or food are prevented, with incidental benefits for transplantation (5, 15), but also favoring HCV and HBV persistence resulting in fibrosis/cirrhosis (2, 491). The tolerogenic MPS phenotype includes moderate surface MHCII (424) with little co-stimulatory CD80/CD86 (438) and immunosuppressive factor expression including PDL-1 (344) and MERTK (482), combined with IL-10 and TGFβ production(3, 5, 14, 15, 17, 32, 344). KC, DC, and LSEC numbers and immunoregulatory state are closely linked with the gut microbiome (11, 492, 493) and influenced by pattern recognition receptors (PRR) including NOD-like and Toll- like receptors (TLR2-4 and TLR9) (433, 492, 494). PRR report the stream of microbial-associated molecular patterns (MAMPs) in sinusoidal blood, such as endotoxin and flagellin (2, 495, 496). Depletion of lymphocyte substrates (e.g. arginase) and vasoactive molecule secretion (adenosine) promote tolerance as an ancillary benefit (Figure 5). Even during inflammation, factors such as contact with

activated stellate cells promote tolerance (326). Nevertheless, the resting state is not innocuous, as liver deprived of MAMP stimulation shows less reperfusion injury (496).

Recent reviews(2, 3, 5, 13-15, 361, 497-499) attribute “liver *allograft* tolerance” to: 1) donor hematopoietic properties, including: a) long-term microchimerism(225, 230, 366, 500); b) activation-induced deletion of recipient effector lymphocytes(361, 362); and c) deficient antigen presentation because of low-level MHC and co-stimulator and/or enhanced inhibitory molecule expression(501); 2) recipient lymphocyte activation by other “tolerogenic” APC (e.g. LSEC, KC, stellate cells, myeloid suppressor cells, hepatocytes) causing apoptosis of effector cells, anergy, exhaustion/senescence, and/or Treg generation (Figure 5); and 3) large antigen load including soluble donor MHC class I molecule secretion (2, 3, 5, 13-15, 361, 497-499). Indeed, chronic exposure (>5 years) to high antigen load appears to contribute to lymphocyte senescence and operational tolerance(502-504) and other complications in humans (505).

Early reviews considered potential contributions from donor-specific “enhancing” antibodies (506-508) - a concept largely abandoned in the antibody era of transplantation(509). Mechanistic theories for regulatory antibody roles include antigen reactive cell opsinization(ARCO)(506-508) and Fc binding and immune complex formation(510, 511). Indeed, Hepatology has mostly viewed antibodies as “biomarkers” but not relevant effectors – dismissing their pathogenic potential despite decades-old (21, 512) and recent evidence to the contrary in acute(513) and chronic settings(167, 514).

Operationally “tolerant” human liver allograft recipients often harbor circulating DSA (186, 515) and might not be considered “truly tolerant” by basic immunologists. However, overt tissue damage is not always observed in this setting(186), similar to “tolerant” rodent liver(506), “enhanced” rodent kidney allograft recipients, and enhanced tumor models (508). All show circulating class II DSA, but a histologically normal graft or non-rejected tumor (506-508). The failure to translate rodent enhancement protocols to patients has been attributed to lack of microvascular capillary class II expression in rodents, contrasted with its presence in humans (506-508). Whether DSA+ “tolerant” liver allograft recipients, who show low-level microvascular MHC class II expression, will eventually indolently manifest DSA-mediated injury and fibrosis in areas not accessible to biopsy or be able to withstand low-level injury because of “defense” mechanisms, described above, is uncertain.

Pathological stimuli that break tolerance include live microorganisms, increased endotoxin and endogenous damage-associated molecular patterns (DAMPs), such as high-mobility group box 1 (HMGB1) from hepatocytes after preservation-related injury, which is sensed by TLR4 (516-520). Such stimuli generate second signals (521) for antigen presentation and T cell activation by KC (increasing CD80 and decreasing PDL-1) (344, 522) and upregulating MHC class II antigens on the microvasculature, perhaps facilitating DSA tissue recognition (76, 199). Interestingly, the presence or absence of an effector response in allogenic tumor enhancement models has been attributed to the amount of tissue complement activation (523). CIITA-induced class II upregulation can also boost tumor recognition(524). These observations highlight the consilience between immune checkpoint regulation in tumor and transplantation immunology(62): the former attempts to activate T cells and/or block inhibitory signaling in contrast to the latter.

Loss of local and systemic Kupffer-dependent tolerance to antigenic particles activate immune responses (344). KC are also capable activators of patrolling

invariant sinusoidal NKT cells (iNKT), by presenting microbial lipid antigens with MHCI-like molecule CD1d (392). The activated iNKT cells arrest, cluster on the KC and produce IFN-γ (392, 525). By releasing CXCL16, KC and monocyte-derived macrophages recruit NKT cells after acute liver injury, which increases monocyte infiltration and fibrogenesis (526). Nevertheless, liver allograft target antigen modulation is a reasonable approach to treatment of chronic AMR.

SUMMARY AND FUTURE DIRECTIONS

The principle of "form follows function" originally coined by American architect, Louis Sullivan, holds true for hepatic immune anatomy. The positioning and microcirculatory design expedite interaction: a) with the external environment delivered via the gut/splanchnic circulation; and b) between innate and adaptive immunity. Byproducts are then exported via the lymphatics or bile. Cellular interactions and outcome have been extensively studied and cells cast as primary agents of liver injury. Antibodies are relegated to a biomarker-only role, signaling systemic immune activation, but recent evidence argues against this viewpoint, at least in allograft livers.

Specific molecular pathways discussed above have been associated with hepatic-based tolerogenic T cell signaling in non-transplant settings and validly projected on to an understanding of "hepatic allograft tolerogenicity". However, a knowledge gap is shown by inability to reliably translate these principles to patients. Instead, an accelerating phase of observational/discovery science has come to rely increasingly on large data sets and cross-platform analyses. This gap might be minimized by applying lessons learned in tumor immunology, which mirror images transplantation immunology.

Insufficient attention to basic biology and hypothesis-testing science and becoming mired in ever increasing detail without a "systems" understanding will likely slow further development. For example, decades-old knowledge that anti-donor antibodies are present in "tolerant" rodent liver allograft recipients led to an incomplete understanding and search for biomarkers in "tolerant" human liver allograft recipients. Therefore, a better understanding of MPS biology, parallels between cancer and transplantation immunology, MHC class II antigen regulation and their relationship to qualitative and quantitative composition of gut microbiome, gut-derived hormones, diet, and medications should receive increasing attention.

Thus, liver allograft immunology will assuredly embrace "discovery science" platforms, but integrate findings into structural-functional relationships.

Figure 1. Hepatic Artery and Biliary Tree

(A) Gross view of the “tolerogenic” hepatic parenchyma enveloping the centrally- p laced biliary tree, which are usefully conceptualized as 2 interdependent organs. The common hepatic duct (blue) bifurcates to hepatic ducts (yellow), which branch to segmental (red; 0.4-0.8 mm) then area ducts with their branches (green; 0.3-0.4 mm). These first generation branches are macroscopically visible “large intrahepatic bile ducts”. A further 7-8 branchings generate septal (>0.1 mm) and interlobular ducts, culminating at ductules and canals of Hering. (B) Extra-hepatic and large intra-hepatic bile ducts contain rows of anastomosing peri-biliary glands that produce mucous and serous secretions. (C) Cross-section of a large intra-hepatic portal tract showing afferent layer of the peri-biliary capillary plexus (PCP; IPEX: brown) that lies immediately beneath the single layer of BEC (IPEX stain for AE1/3: red), shown at higher magnification in the lower right inset. (D) High power magnification of actual terminal portal tract: note the continued close association between capillaries (brown) and the BEC (red).

Figure 2. Microvascular lobular architecture

A 3-dimensional (3D) idealized view of a ***classic hepatic lobule*** (right panel) is formed by ***terminal portal tracts (PT)*** at the vertices of a roughly hexagonal structure, which notionally carry PV parenchymal and HA branches, BD, nerves and lymph channels surrounded by fibrosis tissue (left upper and middle panels (1)). This anatomic design contributes to histologic patterns in vascular disease and functional hepatocyte specialization zones (A: periportal; B: midzonal; and C: perivenular or centrilobular). The figure omits some elements of curvature and variations around large conducting portal vein branches for simplicity.

Figure 3. Hepatic Arterial Buffer Response

The hepatic arterial buffer response (HABR) (58, 59). Increased (portal hyperperfusion in reduced-size livers or after partial hepatectomy) or decreased portal venous flow (sclerosis, thrombosis), reciprocally regulates arterial resistance/vasospasm and flow primarily via adenosine, but other mediators are also likely involved (58, 60, 61).

Figure 4. Hepatic MPS System and hepatic sinusoid structure

Recipient leukocytes from arterial and portal venous blood and pass from portal tracts into sinusoid lumens dressed with relatively static resident macrophages - KC. Slow flowing blood in the highly branched sinusoids is extensively sampled by KC for particulate matter (damaged red cells, immune complexes, opsonized particles), live organisms and soluble signals such as MAMPS from the gut microbiome. KC

defenses to blood-borne infection are heavily integrated with other innate systems including platelets and granulocytes.

Traffic patterns of immature classical/myeloid and plasmacytoid DC and monocytes (see text for details). In steady state, most transmigrated monocytes develop a tolerogenic phagocytic phenotype and traffic along Disse's space to portal tract lymphatics. Some transmigrated monocytes reverse-migrate back into sinusoids (becoming CD16+) as motile cells with pro-inflammatory immune activating and sentinel functions. Monocyte-derived cells can transport antigen to lymphatics, differentiate to tissue macrophages or to monocyte-derived DC. This supply system becomes massively upregulated after liver injury or infection to generate inflammatory infiltrates, including rejection and specialized inflammatory structures such as granulomas and intrahepatic myeloid cell aggregates for T cell population expansion (iMATEs).

Figure 5. Hepatic Tolerance Mechanisms

Hepatic immune reactivity accommodates the rich stream of mostly innocuous portal venous blood with food and microbial antigens, while retaining sensitivity to genuine danger signals from live organisms and/or tissue damage. Efficient circulating particle clearance is led by Kupffer cells; scavenging is combined with immune sensor functions in Kupffer, dendritic and LSEC. Cell responses show a predisposition to tolerance mediated by a self-regulating network of cell intrinsic (epigenetic), soluble microenvironmental (TGFβ, IL-10) and cell surface states (relatively low MHCII and co-stimulators, negative immune regulators such as PDL-1), as discussed in the text.

Abbreviations: PDL-1, programmed death ligand-1; T_{reg}, regulatory T cell; NKT cell, natural killer T cell; PDC, plasmacytoid dendritic cell; LSECtin, liver and lymph node sinusoidal endothelial C-type lectin; CD95L, CD95 ligand; PGE_2, prostaglandin E_2; TGFβ, transforming growth factor β; L, lymphatic; TNF, tumor necrosis factor; ROS, reactive oxygen species.

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Figure `1.

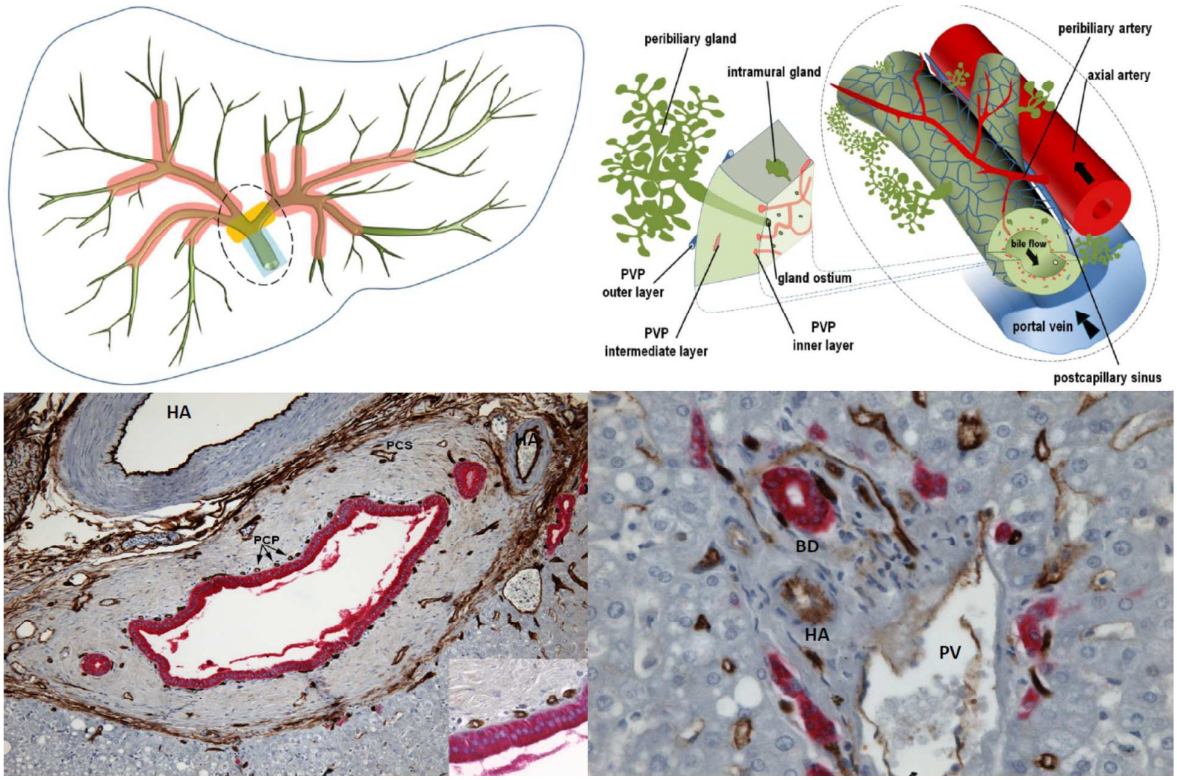
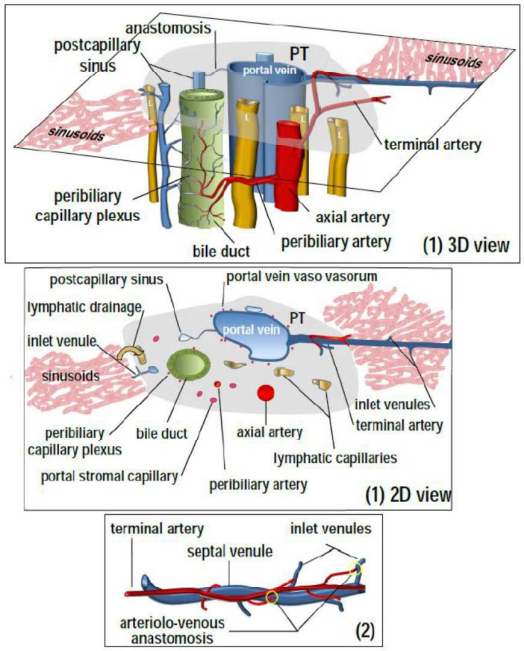

peribiliary gland
intramural gland
peribiliary artery
axial artery
bile flow
PVP
outer layer
gland ostium
PVP
intermediate layer
PVP
inner layer
portal vein
postcapillary sinus
HA
PCS
HA
PCP
BD
HA
PV

Figure 2.


anastomosis
postcapillary sinus
PT
portal vein
sinusoids
sinusoids
terminal artery
peribiliary capillary plexus
axial artery
peribiliary artery
bile duct
(1) 3D view
postcapillary sinus
portal vein vaso vasorum
lymphatic drainage
PT
portal vein
inlet venule
sinusoids
inlet venules
terminal artery
peribiliary capillary plexus
bile duct
axial artery
lymphatic capillaries
portal stromal capillary
peribiliary artery
(1) 2D view
terminal artery
inlet venules
septal venule
arteriolo-venous anastomosis
(2)

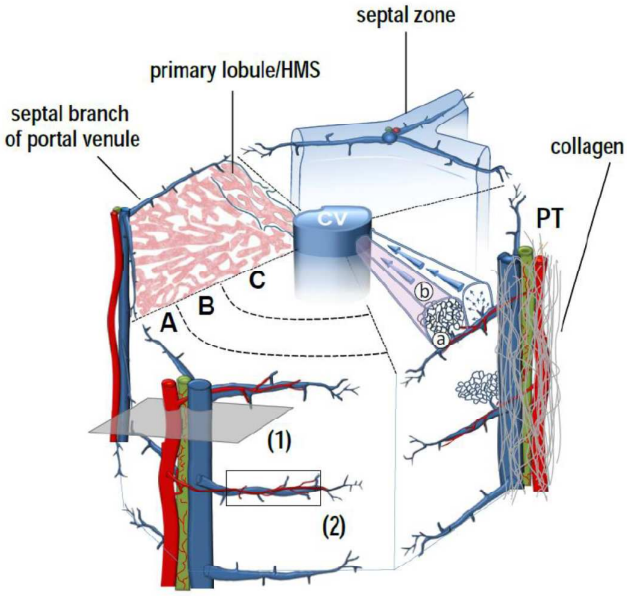

septal zone
primary lobule/HMS
septal branch of portal venule
collagen
CV
PT
C
B
A
b
a
(1)
(2)

Figure 3.

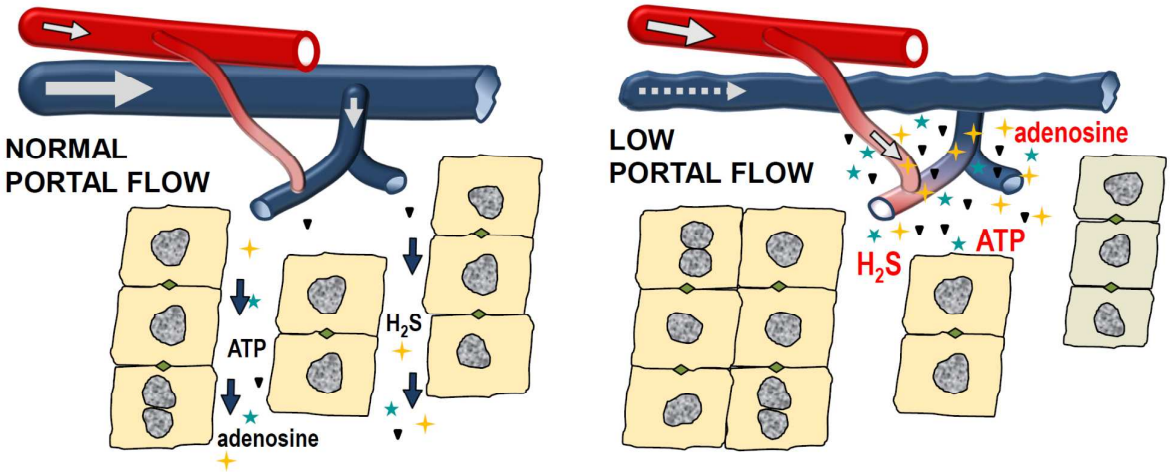

NORMAL
PORTAL FLOW
ATP
adenosine
H_2S
LOW
PORTAL FLOW
adenosine
ATP
H_2S

Figure 4.

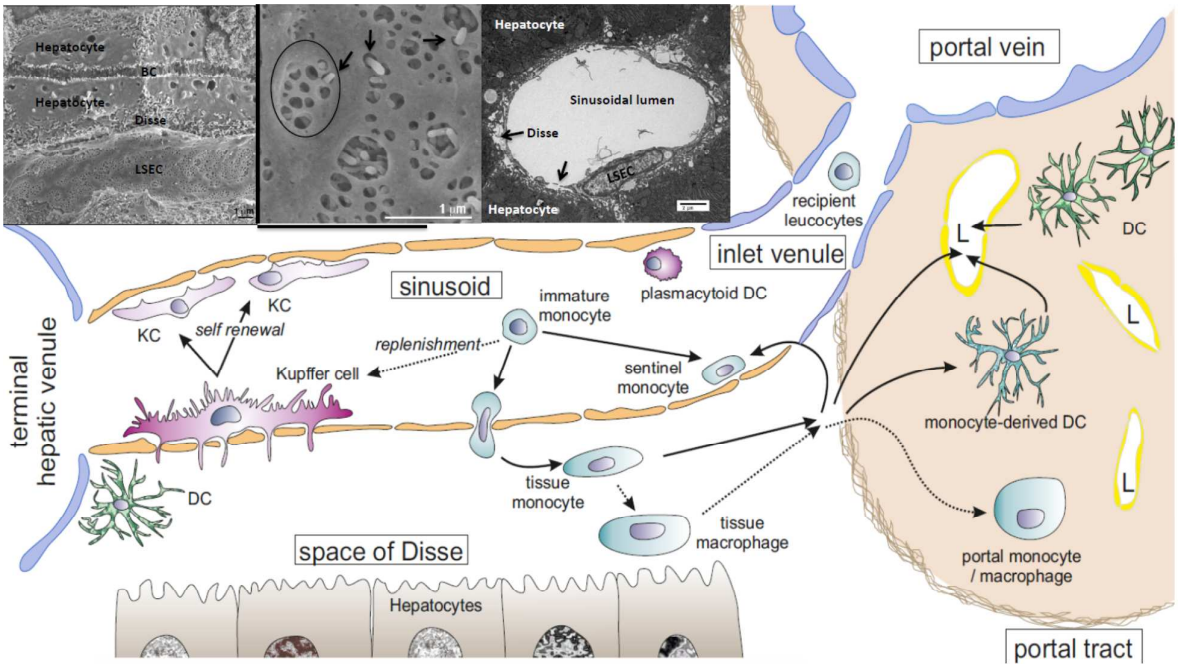
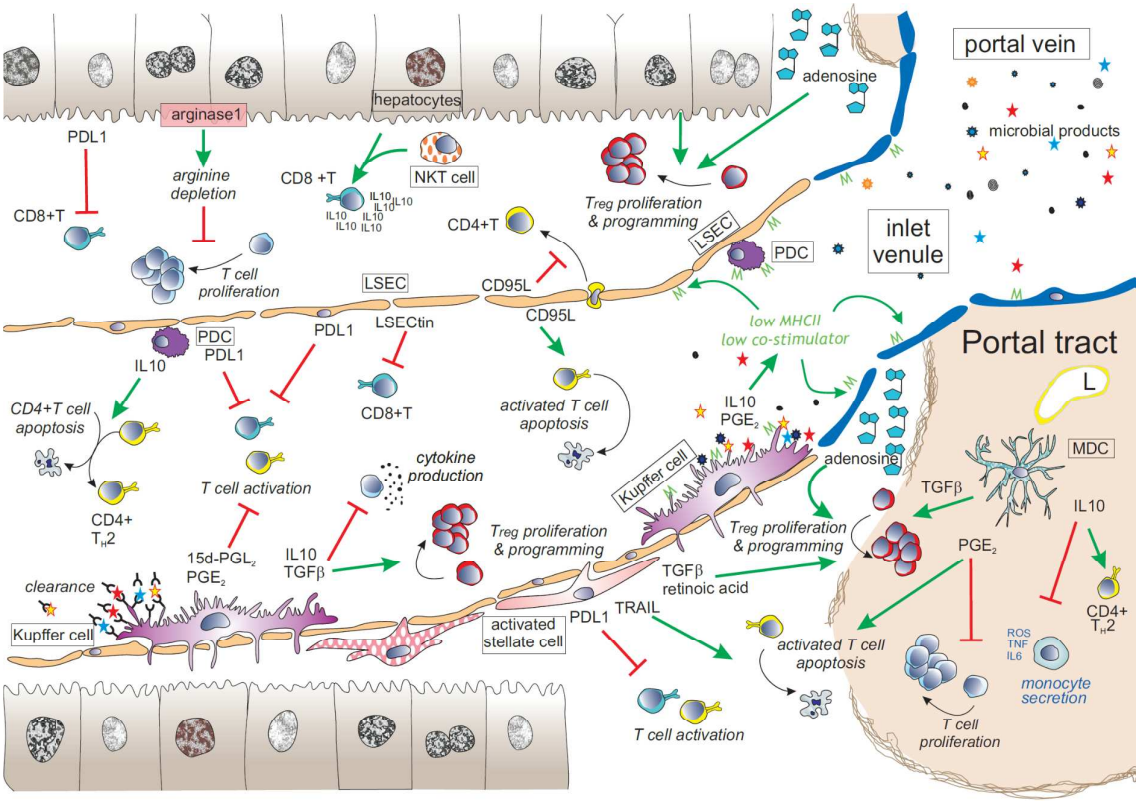

Hepatocyte
BC
Hepatocyte
Disse
LSEC
Hepatocyte
Sinusoidal lumen
Disse
LSEC
Hepatocyte
portal vein
recipient leucocytes
inlet venule
DC
L
L
L
sinusoid
plasmacytoid DC
immature monocyte
KC
KC
self renewal
replenishment
Kupffer cell
sentinel monocyte
terminal hepatic venule
monocyte-derived DC
DC
tissue monocyte
tissue macrophage
portal monocyte / macrophage
space of Disse
Hepatocytes
portal tract

Figure 5.


portal vein
microbial products
adenosine
hepatocytes
arginase1
PDL1
arginine depletion
CD8+T
CD8 +T
NKT cell
IL10
Treg proliferation & programming
CD4+T
LSEC
PDC
inlet venule
T cell proliferation
CD95L
low MHCII
low co-stimulator
Portal tract
IL10
PDC
PDL1
LSECtin
CD8+T
activated T cell apoptosis
IL10
PGE2
CD4+T cell apoptosis
T cell activation
cytokine production
Kupffer cell
adenosine
L
MDC
TGFβ
IL10
CD4+ TH2
15d-PGL2
PGE2
IL10
TGFβ
Treg proliferation & programming
Treg proliferation & programming
PGE2
clearance
Kupffer cell
activated stellate cell
PDL1
TRAIL
TGFβ
retinoic acid
activated T cell apoptosis
ROS
TNF
IL6
monocyte secretion
T cell activation
T cell proliferation
CD4+ TH2

Tables and Figures

Table 1. Expression of ABH and MHC antigens in human liver under normal circumstances versus inflammatory conditions (normal → inflamed liver).

Antigen	HC	BEC	LSEC	KC	SC	HA/PV/CV Endothelium	DC	Portal Microvascular Endo.
AB	–	+	+	–	–	+++	–	++
H	–	++	+	–	–	+++	–	++
MHC A,B	+/- → +	+++	++	++	+→++	++	++	++
MHC DR	- → +	– → ++	– → ++	+→++	+→++	–→++	++→+++	+/- (variable)→+++
MHC DP	- → +	– → +	– → +	+→++	–→+/-	–→++	++→+++	+/–→++
MHC DQ	- → -	–/+ → –	–/+ → –	+→++	–→+/-	–→+/–	++→+++	-/+→++

Abbreviations: BEC: biliary epithelial cells; CV: central vein; DC: dendritic cells; HA: hepatic artery; HC: hepatocytes; KC: Kupffer cells; LSEC: liver sinusoidal endothelial cells; PV: portal vein; SC: stellate cells; Data compiled from references ((202-207, 210-215, 226, 527-529)). More work in needed in study class II expression in specific compartments.